Self-Assembled Coatings for Controlling Biomolecular Adsorption on Surfaces

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Abstract—**We have investigated a series of molecular and polymeric approaches for generating adherent thin films that impart anti-fouling characteristics to oxide surfaces. These films incorporate oligo- or poly(ethylene glycol) moieties that are expressed in high density in the near-surface region. In our molecular approach, oligo(ethylene glycol)-terminated *n*-alkyl-trichlorosilanes, $RO(CH_2CH_2O)_3(CH_2)_{11}SiCl_3$, have been designed so to spontaneously adsorb onto oxide surfaces and produce densely packed films. Another strategy uses a surface initiated polymerization to generate reactive anchored polymer chains that are then chemically modified to incorporate oligo(ethylene glycol) units. Lastly, a comb copolymer comprising a poly(acrylic acid) backbone and different grafting ratios of a linear poly(ethylene oxide-*r*-propylene oxide) chain has been prepared that adsorbs onto surfaces and forms a poly(ethylene glycol)-exposing film in single step. These surface coatings provide varying levels of protein and cellular resistance that can be related to molecular-scale elements of their surface structure.**

***Index Terms*—Polymer coatings, protein adsorption, surface modification, thin films.**

I. Introduction

THE non-specific adsorption of cells, proteins, and other biological species onto surfaces is a problem common to biomedical devices, biochemical processing, and biodiagnostics [1], [2]. This problem is particularly acute for objects made of metal or glass as proteins and other species will often adsorb in multilayer quantities onto their corresponding metal oxide surfaces by electrostatic attraction [3]. Common methods to retard the adsorption include the use of alkyltrichlorosilanes (typically n-$C_{18}H_{37}SiCl_3$) to passivate the glass or metal oxide surface with a covalent hydrocarbon film [4] or the attachment or grafting of poly(ethylene glycol) to the surface [5]-[7]. In the former approach, molecular films from the silane are prepared on the high energy oxide surface to produce a low energy, hydrophobic surface [8]-[10]. The attached hydrocarbon chains reduce the non-specific adsorption of proteins by screening the electrostatic attraction between the underlying material and charged biomolecules such as proteins; however, the hydrophobic surface—by nature of having a relatively high interfacial free energy ($\gamma_{SL} \approx$ 50 mN/m) when contacted with water—will routinely adsorb roughly a monolayer of protein.

Surface-bound poly(ethylene glycol) (PEG) is a common strategy for retarding the non-specific adsorption of proteins and other biological species [11]. Methods for covalently attaching PEG to surfaces include the incorporation of PEG monomers into polymer networks by graft polymerization [12]-[18] and the direct attachment of PEG chains to surfaces by a coupling reaction [11]. In graft polymerization, the PEG chains are incorporated as segments of a polymer backbone, and the incorporated PEGs can have limited effect on non-specific adsorption depending on the surface density of the PEG chains [19], [20]. The direct attachment of PEG chains to a surface provides a superior method for manipulating surface properties; however, multiple processing steps are often required for coupling the PEG molecules to the substrate [21], [22]. For inorganic substrates, silane reagents are often used to present reactive organic moieties (amines, epoxides, isocyanates, etc.) that provide sites for the covalent attachment of PEG chains. In these procedures, the molecules used for attaching PEG chains to these sites frequently include a variety of specialty PEG derivatives [23]—PEG-monoacrylates, PEG-NH_2, PEG-CHO, CH_3O-PEG, PEG epoxides, star-PEGs, etc.—whose availability and cost can limit the utility of this approach. For these procedures, the effectiveness of the resulting coated surface is related to the surface density of PEG chains as uncoated regions that expose the underlying material often provide sites that undergo non-specific protein adsorption [24]. Objects with complex

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morphologies and inner surfaces offer particular challenges for this method of surface modification due to difficulties in producing uniform, defect-free coatings of PEG. Molecular precursors, such as analogs of $CH_3(CH_2)_{17}SiCl_3$ that produce densely packed films spontaneously onto surfaces from solution with high uniformity of coverage [10], could offer distinct advantages over present methods if they exposed a PEG-type surface that retarded the non-specific adsorption of proteins.

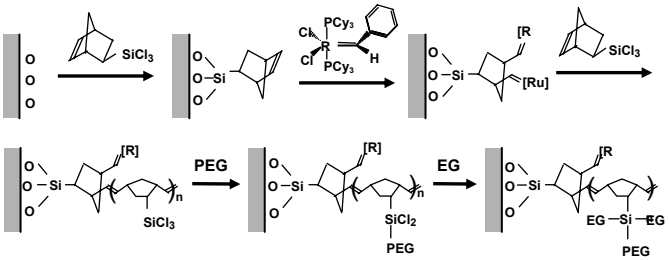
To address this problem of surface modification, we have developed three procedures for producing thin coatings exposing short PEG chains. The first approach (Scheme I) uses reagents that combine the protocol of use of the trichlorosilane-based adsorbates with the generation of oligo(ethylene glycol) (or OEG)-based surfaces to generate robust coatings for glass and metal oxide substrates that are resistant against the non-specific adsorption of various proteins and cells. These reagents are based on the results of

Scheme I

Prime and Whitesides who demonstrated the effectiveness of films formed by the adsorption of $HS(CH_2)_{11}(OCH_2CH_2)_nOR$ (R = H and n = 0-6; R = CH_3 and n = 6) onto gold to retard the non-specific adsorption of proteins [25]. The observation that only a few ethylene glycol units were required in these oriented assemblies to retard protein and cell adsorption and that methyl-terminated ethylene glycol units were also effective provided the basis for our development of oligo(ethylene glycol)-terminated silane reagents and other approaches that would localize these groups at outer surfaces. The methyl cap is needed on the ethylene glycol group for generation of a silane-based reagent that could be used on glass and metal oxide substrates as the hydroxyl group of an ethylene glycol cannot be accommodated within a molecule bearing a trichlorosilyl group due to their cross reactivity. In general, trichlorosilane reagents are useful for functionalizing a broad class of substrates (metal oxides) [26], and they are widely used in practical applications as they exhibit useful levels of stability [4], [26].

The second strategy makes use of an approach we developed for growing polymer chains from a surface by an organometallic-catalyzed living polymerization process [27]. Specifically, we adopted a solution-phase ring-opening metathesis polymerization reaction to proceed from reactive sites localized on a surface (Scheme II). By this approach, we could generate a film of attached polymer chains that contain reactive groups along each segment of the chains that we reacted with various ethylene glycol (EG) variants for generating of a dense surface of these groups. We investigated the effects of oligomeric EG chain length on the

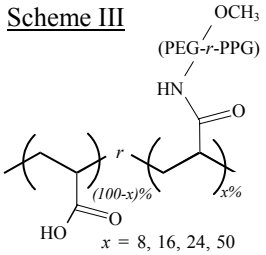
Scheme II



properties of these modified films as well as their anti-fouling characteristics, observing the role that steric factors play in such modifications.

A final strategy is pursued that uses a preformed polymer for surface modification. Here, the polymer contains a polyacrylic acid backbone for adhesion to an oxide surface and poly(ethylene glycol)-containing chains to provide anti-fouling characteristics (Scheme III). For various proteins, this approach provided satisfactory results; however, it proved to exhibit a greater sensitivity to the charged state of the protein than did films formed by other methods. The system reveals the importance of exposing solely ethylene glycol units at the outer surface and the advantages of the other approaches for achieving such structures.

Scheme III



For these three systems, we demonstrate the effectiveness of these coatings for producing robust films that inhibit the non-specific adsorption of proteins. In particular, we examined proteins with molecular weights from 10,000 to 400,000 Da (insulin, lysozyme, albumin, hexokinase, and fibrinogen). We explored the effects that oligo(ethylene glycol content) had on the structure of each system and its adsorptive characteristic.

II. Non-Fouling Molecular Films Formed by Adsorption of Oligo(Ethylene Glycol)-terminated Alkyltrichlorosilanes

A. Protein Repellency

We examined the adsorption properties of the methyl-capped oligo(ethylene glycol)-terminated alkyltrichlorosilane films on Si/SiO_2 by immersing them into various protein-containing solutions at a concentration of 0.25 mg/mL for 24 h at room temperature. The proteins investigated were insulin, lyzozyme, albumin, hexokinase, and fibrinogen. In these solutions, we performed concurrent experiments using surfaces coated with octadecyl chains to allow direct comparisons of the performance of these films with a standard system. The amount of adsorbed protein was determined optically ex situ using ellipsometry. We also used techniques such as x-ray photoelectron spectroscopy (for siloxane and thiolate SAMs) to determine the amount of adsorbed proteins. These techniques are superior to ellipsometry because on their

detection of specific chemical signals—nitrogen composition or amide content—resulting from the protein; however, they required much longer times for characterizing each sample. In general, we found that the thickness data from ellipsometry agreed with results from these other methods, and we used it as our primary characterization method.

Figure 1 summarizes the protein adsorption results on the various surfaces as measured using ellipsometry. The four proteins adsorbed onto the hydrophobic surfaces prepared from octadecyltrichlorosilane, with the higher molecular weight proteins forming thicker adsorbed films. The amounts are lower than adsorbs onto untreated glass surfaces, but the hydrophobizing treatment is not effective in stopping protein adsorption. For these proteins, the measured thicknesses of the film on these surfaces correspond to roughly a monolayer of adsorbed protein suggesting that the proteins adsorb to lower the interfacial energy between the hydrocarbon coating and water and the resulting protein surface does not promote further adsorption.

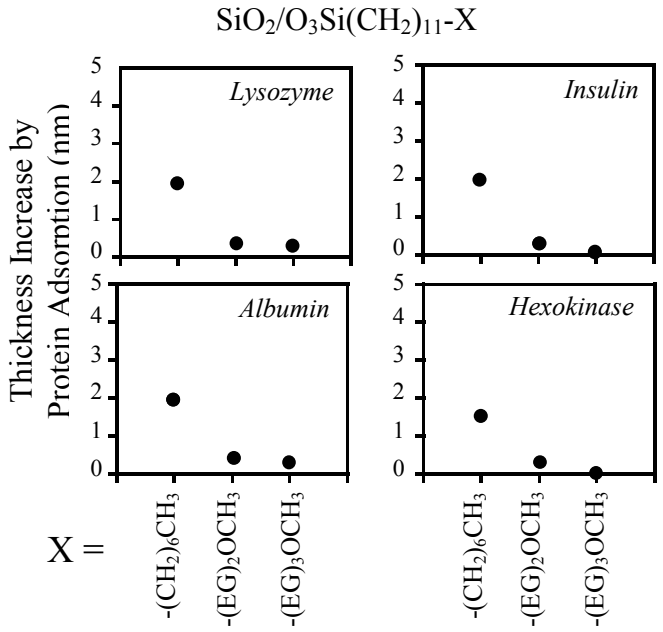


Fig. 1. Ellipsometric thicknesses of adsorbed films of insulin, lysozyme, albumin, hexokinase, and fibrinogen on monolayer surfaces formed from $CH_3(CH_2)_{17}SiCl_3$, $CH_3(OCH_2CH_2)_2O(CH_2)_{11}SiCl_3$, and $CH_3(OCH_2CH_2)_3O(CH_2)_{11}SiCl_3$.

The incorporation of two and three oligo(ethylene glycol) units as linkers between the methyl terminus and the alkyl chain resulted in a notable reduction in the amount of protein adsorption onto the Si/SiO_2 surfaces. For insulin, lysozyme, albumin, and hexokinase, the coatings resisted protein adsorption within the experimental errors of ellipsometry. Complete resistance against the adsorption of fibrinogen was not possible with the $EG_{2,3}$-CH_3 surfaces. The difference in the adsorption characteristics of these EG-CH_3-capped monolayers can be explained partially by the lower interfacial energy of the latter system with water. Entropic effects may also be operative for the oligo(ethylene glycol) system [1], [24]. In many ways, the results on these surfaces mirrored those prepared using similarly substituted *n*-alkanethiols adsorbed as thin films on gold.

In one important difference, the CH_3-capped oligo-(ethylene glycol) films on Si/SiO_2 formed from the silanes adsorbed more fibrinogen than did related thiol-based surfaces with this termination formed on gold. The superior properties on gold may reflect the greater ease for forming oriented, well-defined, self-assembled, thiol-based monolayer films as silane reagents can form polymeric aggregates that can diminish the surface properties of the film [26]. The presence of such aggregates could provide local hydrophobic sites for the adsorption of proteins. As we assembled the silane films under an inert atmosphere and used physical methods to displace any physisorbed materials from the surface, the amount of physisorbed material on our surfaces should be low. Structural differences in the molecular conformation of the CH_3-capped tri(ethylene glycol) layer—crystalline vs. amorphous—have been reported to affect the protein resistance of such surfaces toward fibrinogen and such differences may be operative here [28].

In addition to the ellipsometric results, the wetting properties of the surfaces provided a macroscopic (albeit qualitative) indicator of protein adsorption. The initially prepared surfaces were hydrophobic and emerged dry when rinsed with water. After exposure to the protein solutions, the purely alkyl systems became less hydrophobic, while the oligo(ethylene glycol) surfaces maintained their hydrophobicity. In particular, the receding contact angle of water on surfaces with an adsorbed layer of protein was ~25° and was sufficiently low to provide a visual indication of protein adsorption.

Stability of Films. The practical utility of a coating is based on both its performance and its ability to maintain its useful properties. We examined the stability of the siloxane films by exposing them to various conditions including boiling water, hot hydrocarbon solutions, oven drying, and autoclaving. The films retained their protein resistant properties after immersion in boiling water at 100 °C, in decalin at 90 °C for 1 h, and drying in an oven at 120 °C for 1 h; however, they exhibited significant deterioration after drying in an oven at 200 °C for 1 h. These observations are compatible with the literature regarding the thermal stabilities of siloxane monolayer films as such films are reported to exhibit no detectable changes in structure and wetting properties when heated to ~140 °C and subsequently characterized at room temperature [9], [20]. For our reagents and coatings, the presence of the CH_3-capped oligo(ethylene glycol) tail does not appear to negatively impact the thermal stability of an alkylsiloxane monolayer. For use in applications that require sterilized glassware and silicon-based microfluidic systems, we note the silane-based coatings maintained their integrity and properties after an extended sterilization cycle (1 h) in an autoclave at ~120 °C and (pressure = 20 psi). This ability may make these films suitable for numerous applications where sterile conditions are

required and there are needs to limit the non-specific adsorption of proteins.

III. Non-Fouling Polymer Films formed by Modification of Surface-Initiated Ring-Opening Metathesis Polymers Derived From Norbornenyltrichlorosilane with Oligo(Ethylene Glycol)s

A. Film Formation

Scheme II displayed the general strategy for producing grafted polymer chains on a support by a surface-initiated process based on a ring-opening metathesis polymerization process that we had earlier developed [27]. In this work, we used this reaction process to generate grafted polymer chains on a support where the chains were composed of a repeat unit bearing a reactive functionality that could subsequently be derivatized to contain oligo(ethylene glycol) units. This process was pursued as an approach to generate robust surface coatings that could bear a high density of oligo(ethylene glycol) units needed to convey protein resistance and other anti-(bio)fouling characteristics.

Using norbornenyltrichlorsilane as monomer, the surface-initiated ring-opening metathesis polymerization (ROMP) process generated grafted polymer films with thicknesses ranging from 50 to 150 nm depending on the reaction conditions. In general, the polymerization reaction proceeded for up to 1 hr before chain termination and other deactivation processes ended surface activity for polymerization. The most commonly employed condition involved soaking a norbornenyl surface in a 4 mM solution of the bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride $(Cy_3P)_2Cl_2Ru{=}CHPh$, Cy = cyclohexyl] catalyst in methylene chloride for 20 min and then forming the polymers by transferring this catalyst-containing surface to a 25 mM solution of norbornenyltrichlorosilane in methylene chloride for 80 min.

B. Protein Repellency

A key question in the derivatization of these grafted poly(norbonenyltrichlorosilane) films with oligo(ethylene glycol)s (OEGs) was whether longer or short chain variants would yield a higher surface density of the ethylene glycol units. Figure 2 shows two anticipated extremes of behaviors for use of a long and a short OEG. With longer OEGs, steric restrictions may limit reaction between trichlorosilane side chain groups and the OEG to surface sites whereas shorter OEGs may be able to penetrate into the polymer chain coating and generate an effectively thicker film in the near surface reaction. We surveyed the properties of films prepared using a series of OEGs with differing molecular weights and observed the thickest OEG layer using a OEG with a molecular weight of 300. Further improvements in OEG density could be obtained by immersing these reacted surfaces with ethylene glycol—a very small OEG variant—to fill sterically inaccessible sites. By this two-step strategy, we generated near-surface OEG coatings that were ~3.5 nm in thickness.

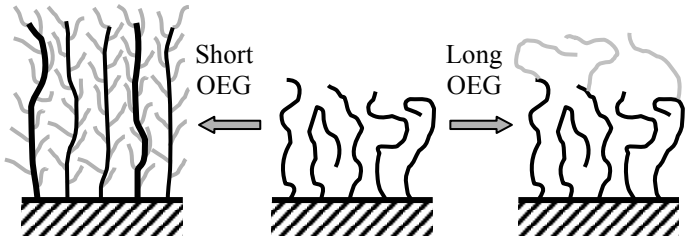


Fig. 2. The central image schematically displays a grafted poly(norbornenyl-trichlorosilane) film formed by surface-initiated ROMP and the possible products formed by reacting this film with short-chain and long-chain oligo(ethylene glycol)s (OEGs).

The utility of these films lie in their ability to limit protein adsorption. Figure 3 displays representative data obtained by x-ray photoelectron spectroscopy for the adsorption of fibrinogen onto various surfaces. Fibrinogen is a particularly challenging protein in the engineering of protein resistant surface as it is responsible for coagulation and tends to adsorb indiscriminately onto most surfaces. The figure clearly shows that the derivatized surfaces are effective at reducing the adsorption of this protein, with the use of ethylene glycol in a second step to fill in open sites providing additional antifouling abilities.

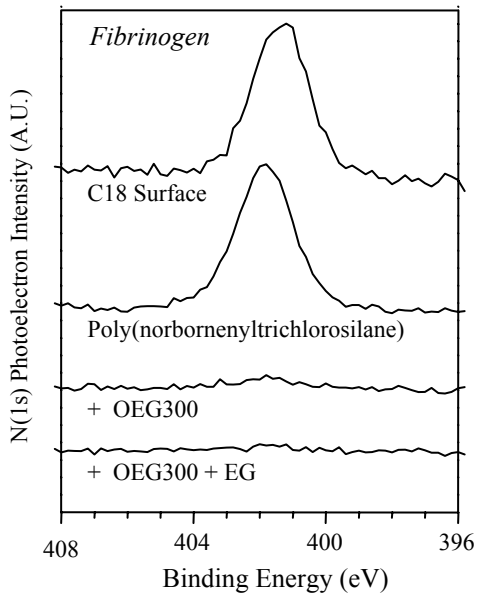


Fig. 3. X-ray photoelectron spectroscopy intensities from nitrogen signals (N(1s) from adsorbed fibrinogen on a model hydrophobic surface (C_{18}), the native ROMP poly(norbornenyl trichlorosilane) polymer and variants derivatized with a 300 molecular weight oligo(ethylene glycol) and also with ethylene glycol. Lower intensities signify less protein adsorption.

Figure 4 displays the nonspecific adsorption results across four proteins (fibrinogen, hexokinase, insulin, and lyzozyme) on a variety of surfaces. For the various OEG-modified surfaces, the least amounts of protein adsorption occurred with those modified with the 300 molecular weight OEG. The use of this OEG generated the thickest OEG film on the ROMP polymer surfaces. In constrast with the adosrption

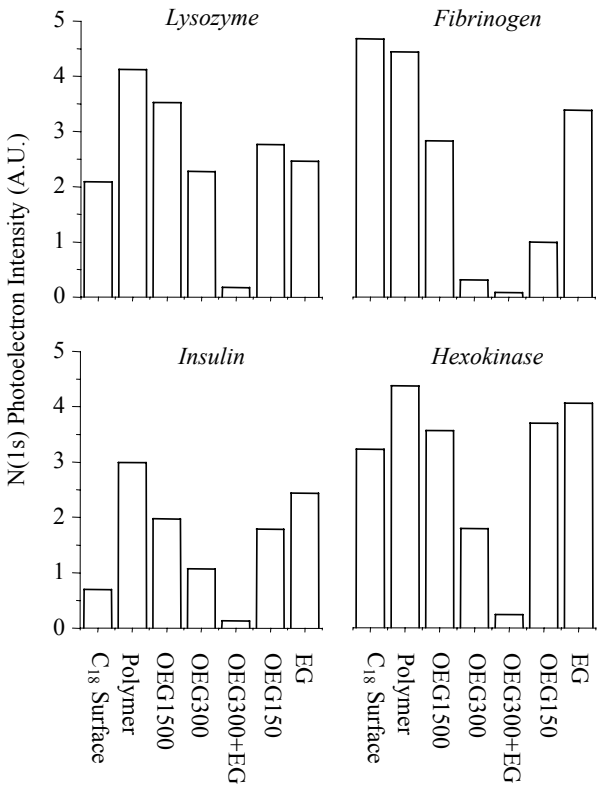


Fig. 4. X-ray photoelectron spectroscopy results for the adsorption of lyzozyme, fibrinogen, insulin, and hexokinase onto a model C_{18} surface, a native poly(norbornenyl trichlorosilane) film ("Polymer") and variants of this polymer modified with ethylene glycol (EG) or an oligo(ethylene glycol (OEG), with one sample being modified sequentially with both an OEG and EG. This last film exhibited the lowest amounts of protein adsorption.

results for fibrinogen (Figs. 3 and 4), the reductions in adsorption for the three other proteins by this modification were more modest and showed less dramatic differences from those by the other OEGs. The lowest levels of protein adsorption showed a correspondence to the thicker OEG films. Treatment of the ROMP-derived poly(norbornenyl trichlorosilane) films first with 300 molecular weight OEG and then with ethylene glycol generated films with the thickest OEG films and the best abilities to retard protein adsorption (Figure 4). This attribute appeared universal across the examined proteins and suggests much promise for these films.

IV. Non-Fouling Polymer Films formed by Adsorption of Comb Copolymers with a Polyacrylic Acid Backbone and Grafted Poly(ethylene glycol)-*R*-poly(propylene Glycol) Linear Chains

A. Film Formation

We pursued a strategy whereby a polymeric coating could be assembled onto a surface by its spontaneous adsorption onto a substrate. To accomplish this goal, we designed a polymer that included a poly(acrylic acid) (PAA) backbone as carboxylic acid groups readily coordinate to metal oxide and amine surfaces. The multiple coordination sites available by use of a polymer produce adsorbed films with good stability. To produce the desired anti-fouling characteristics, we targeted inclusion of grafted poly(ethylene glycol) chains to the PAA backbone as end-immobilized brushes in order to provide maximal entropic freedom to the system. These chains would not adsorb onto the oxide or amine surface and thus be excluded from the underlying surface to be expressed as the outer surface. For economic reasons, we employed a commercially available linear copolymer that terminated in an amine at one end (for attachment to PAA), a methoxy group at its other end (an inert chemical group), and a linear backbone that was rich in poly(ethylene glycol) units (86%) with the remainder being poly(propylene glycol) units. This random heteropolymer has been used in cement formulation and can be obtained cheaply and in bulk in contrast with the homopolymer analog which is an expensive specialty polymer. In our work, we found that this broadly available heteropolymer could be emplyed to provide properties typically viewed as possible with the homopolymer.

We prepared comb polymers of the structures shown in Scheme III by grafting various densities of the H_2N-[poly(ethylene glycol)-*R*-poly(propylene glycol)]-OCH_3 onto PAA (molecular weight = 5000) via a one-step, one-pot amidation reaction. These polymers were adsorbed directly onto glass surfaces or glass surfaces treated to expose an amine surface (using the amino-silanating reagent AHPTS) by simply dipping the surface into an aqueous solution of the comb polymer. This process formed films that were ~1 nm in thickness. Films formed from comb polymers with higher grafting densities of the poly(ethylene glycol)-*R*-poly(propylene glycol) formed thicker films and that expressed greater amount of poly(ethylene glycol) at their surface.

B. Protein and CellRepellency

Figure 5 compares the non-specific adsorption results for four proteins (fibrinogen, hexokinase, insulin, and lyzozyme) onto bare glass surfaces and surfaces that were coated with a nanometer-thick coating of the comb polymer. The films were self-assembled onto the substrates by an adsorption process. The results in Figure 5 show that the comb polymer was effective at retarding the non-specific adsorption of insulin, and was able to reduce the non-specific adsorption of the other proteins from that on glass. The coatings show the general trend of a better ability to retard protein adsorption as the grafting density of the poly(ethylene glycol)-*R*-poly(propylene glycol) chains on the PAA backbone increased. This effect can be ascribed to the ability to generater thicker coatings (i.e., less exposed glass) and a lower density of exposed carboxylic acid groups that could play a role in protein adsorption. For example, the adsorption of lyzozyme onto these polymer surfaces was greater than expected and could be due to lyzozyme having a positive charge at the pH (7.4) employed for the adsorption experiments.

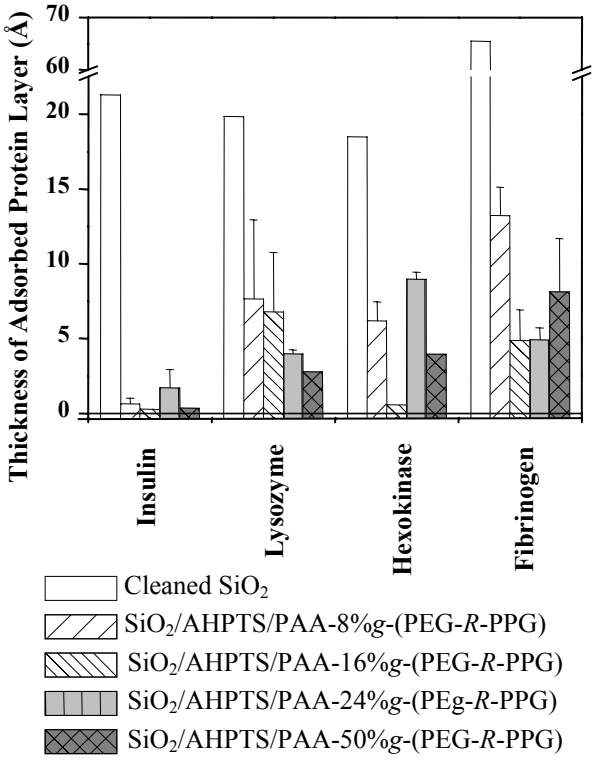


Fig. 5. Ellipsometric thicknesses of non-specifically adsorbed protein layers formed by exposing cleaned and treated SiO_2 surfaces to various protein solutions (0.25 mg/mL at pH = 7.4) for 24 h. The treated SiO_2 surfaces were first derivatized with an amino silanating agent (AHPTS) and then exposed to an aqueous solution of a comb copolymer comprising a poly(acrylic acid) (PAA) backbone and various grafting densities (*g*%) of a random linear poly(ethylene glycol)-poly(propylene glycol) (PEG-PPG) copolymer.

We have begun examining the abilities of these films to retard the adsorption of cells onto glass surfaces and Figure 6 shows some representative results for surfaces in contact with *E. coli*. The results show a large amount of cellular aggregation on the bare glass surface as well as onto the poly(acrylic acid) (PAA) film. For the films that exposed poly(ethylene glycol) groups, the films were able to greatly retard the cell adsorption.

Films formed from these comb polymers, by using a collection of carboxylic acid along the PAA backbone for adhesion, show good stability. The films are stable to boiling water, high salt concentrations, and sonication, suggesting that these films—easily prepared, polymers easily synthesized, films showing robust behavior and useful antifouling characteristics—have potential for being broadly useful in a number of medical and biotechnological applications. Current efforts focus on improving their antifouling characteristics and studying the structure of these nanometer-thick coatings.

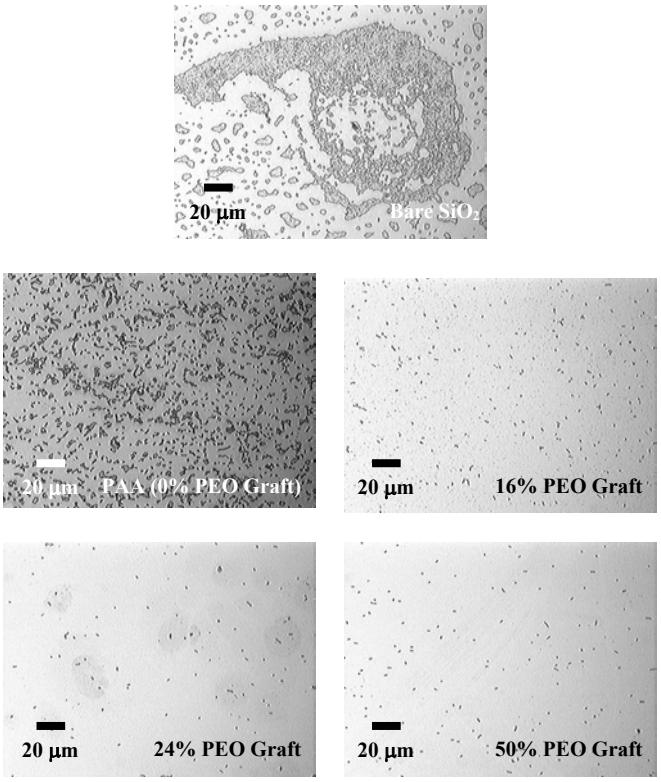


Fig. 6. Representative optical microscopy images of non-specifically adsorbed *E. Coli* cells on native (top image) and treated SiO_2 surfaces. The treated SiO_2 surfaces were first derivatized with an amino silanating agent (AHPTS) and then exposed to an aqueous solution of a comb copolymer comprising a poly(acrylic acid) (PAA) backbone and various grafting densities of a random linear poly(ethylene glycol)-poly(propylene glycol) (PEG-PPG) copolymer. The polymer films containing 24 and 50% grafting densities showed promising cell resistance characteristics and greatly improved properties over those of untreated SiO_2 surfaces and those treated with pure PAA.

V. Conclusion

Molecular-scale engineering of interfaces as an approach for localizing requisite chemical functionalities at surfaces is a useful strategy for tailoring properties. Antifouling characteristics can be imparted to a surface by localizing nanometer-thick films of poly(ethylene glycol) in the outermost accessible region of a substrate. Self-assembly and surface initiated polymerization routes provide convenient methods for introducing such coatings, where their stability can be designed into the film by selection of the anchoring chemistry. The described methods are flexible, offer the abilty to coat a broad class of surface morphologies, and scalable. Initial results suggest promise for the use of such coatings for reducing protein as well as cellular adsorption onto oxide surfaces.

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